Original Article

Comparison of size of the liver between patients with non-alcoholic fatty liver disease and healthy controls

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Abstract

Background: Non-alcoholic fatty liver disease (NAFLD) is the most common chronic liver disease across all age groups. Limited studies have been conducted to consider the relationship between NAFLD and liver size. This study aimed to compare the size of the liver between NAFLD patients and healthy controls. **Methods:** This case-control study was conducted on NAFLD patients ($n = 300$), and healthy subjects ($n = 300$) referred to the Golestan Hospital of Ahvaz from April to August 2021. All individuals underwent ultrasonography examination, and liver size was measured in the midclavicular line. Fatty liver was divided into three grades, I (mild), II (moderate), and III (severe), according to the disease severity. Anthropometric parameters, including age, sex, weight, height, and body mass index (BMI), were recorded. Finally, the size of the liver and its relationship with NAFLD and anthropometric parameters was evaluated. **Results:** Patients had significantly higher weight, and BMI mean values than controls ($P < 0.001$). In comparison to controls, NAFLD patients had considerably larger livers on average. (149.05 ± 12.60 mm vs. 134.51 ± 12.09; $P < 0.001$). There was a significant tendency for larger liver size in normal to severe fatty liver patients ($P < 0.001$). In patients with mild, moderate, and severe NAFLD, the mean liver size was 144.34 ± 11.35, 154.21 ± 10.84, and 158.63 ± 13.45 mm, respectively. The mean liver size in both groups was significantly higher in males than females ($P < 0.05$). Age ($P = 0.037$), sex ($P < 0.001$), height ($P < 0.001$), BMI ($P = 0.008$), and steatosis ($P < 0.001$) were independent variables for predicting the liver size. **Conclusion:** The liver size of persons with fatty liver was substantially more considerable than healthy people. The size of the liver was substantially linked with sex, age, BMI, fatty liver, and hepatic steatosis grade. A straightforward way to predict fatty liver is to use ultrasonography to determine the size of the liver.

Keywords: Body mass index, metabolic disorders, non-alcoholic fatty liver disease, ultrasonography

Introduction

Non-alcoholic fatty liver (NAFLD) is one of the most common metabolic disorders worldwide and is associated with excess lipid accumulation in the liver cells. NAFLD affects about 20–30% of the general population in Western countries.[1] NAFLD prevalence in Iran varied from 4 to 40%.[2] Obesity, diabetes, insulin resistance, and hyperlipidemia are the most critical risk factors for NAFLD.[3] NAFLD encompasses not just a broad spectrum of liver diseases such as steatosis, cirrhosis, and end-stage liver disease,[4-6] but it has also been linked to insulin resistance, dyslipidemia, diabetes mellitus, and cardiovascular disease.[7] Liver fibrosis and hepatocellular carcinoma are the major life-threatening consequences of NAFLD in these patients.[8] Previous studies reported that the incidence of hepatocellular carcinoma in patients with NAFLD is about 0.44 per 1000 people.[9]

Although liver biopsy has remained the gold standard for diagnosing NAFLD, its use is limited due to the invasive

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Received: 13-01-2023 **Revised:** 11-02-2023
Accepted: 01-06-2023 **Published:** 06-03-2024

Access this article online

Quick Response Code:

Website: http://journals.lww.com/JFMPC

DOI: 10.4103/jfmpc.jfmpc_94_23

How to cite this article: Dorostghol M, Gharibvand MM, Hanafi MG, Motamedfar A. Comparison of the size of liver between patients with non-alcoholic fatty liver disease and healthy controls. J Family Med Prim Care 2024;13:425-30.

nature of the operation.[10] Among ultrasound, CT scan, and MRI techniques, ultrasound is a painless, non-invasive imaging technology for detecting fatty liver.[11] On ultrasound examination, infiltration varies depending on the amount of fat and whether the fat deposit is diffuse or focal. Diffuse steatosis can occur as mild, moderate, or severe types.

Mild liver steatosis is characterized by a slight increase in hepatic echogenicity in the presence of a standard diaphragm and peripheral vascular margin. Moderate liver steatosis is characterized by a bit of rising in hepatic echogenicity and a slight difficulty seeing the diaphragm and the intrahepatic artery margin. Severe steatosis is characterized by a rise in hepatic echogenicity and poor penetration into the posterior parts of the right lobe of the liver and the hepatic arteries.[12]

Ultrasound could be used to predict NAFLD in a non-invasive and reliable manner. Recent research has shown that liver size changes occur in a variety of clinical disorders, including fatty liver, and that evaluating liver size can be a valuable tool for diagnosing hepatic diseases.[13] For this reason, some studies have been conducted to examine the size of the liver in NAFLD patients and normal groups.[14-16] Furthermore, taking into account the impact of numerous risk factors and anthropometric measures on liver size might assist predict fatty liver risk in a population. We designed this study to evaluate the effect of fatty liver disease and its severity on the liver size on ultrasound examination because there has been a limited number of studies and conflicting findings on the association between NAFLD and liver size. Furthermore, the relationship between anthropometric parameters and liver size and their importance for predicting NAFLD occurrence was evaluated.

Materials and Methods

Study population

Patients with definitive NAFLD based on sonography findings and aged between 18 and 65 years old were entered into the study. The exclusion criteria were as follows (i) history of opiate use (e.g., smoking and alcohol consumption), (ii) age <18 years old, (iii) history of viral hepatitis (A, B, and C) or other liver diseases, (iv) taking hepatotoxic drugs and steroids, and (v) patients with incomplete anthropometric information. Demographic and basic clinical information of individuals, such as age, sex, weight, height, and body mass index (BMI), were recorded for all subjects. All patients signed informed consent before the study.

Study design

This case-control study was conducted on patients with NAFLD and healthy individuals referred to Golestan Hospital of Ahvaz (Ahvaz, Iran) from April to August 2021. The Ethics Committee approved the study of the Jundishapur University of Medical Sciences (IR.AJUMS.HGOLESTAN.REC.1399.174).

Fatty liver diagnosis and classification

Fatty liver was characterized by increased diffusion of the liver parenchyma to the kidney, which was opaque and had deep-echo attenuation. Fatty liver was graded based on the amount of fat accumulation in the liver cells and increased liver echogenicity compared to normal under ultrasonography. According to the disease severity, the fatty liver was divided into three grades I, II, and III. Grade I (mild steatosis) is characterized by a slight increase in hepatic echogenicity with standard diaphragm and margin of intrahepatic vessels. Grade II (moderate steatosis) is associated with a slight increase in hepatic echogenicity and slight difficulty seeing the diaphragm and margin of intrahepatic vessels. Grade III (severe steatosis) is characterized by a significant increase in echogenicity with poor penetration into the posterior parts of the right lobe of the liver and hepatic arteries. Finally, the size of the liver and its relationship with other basic demographic and clinical data of the patients and controls were evaluated. The craniocaudal liver length at the midclavicular line was measured. The measurement was made from the dome of the diaphragm during deep inspiration.

Ultrasonography

Individuals in the patient and control groups underwent abdominal ultrasounds (GE Healthcare Voluson E6). Abdominal ultrasound was performed with a 2–5 MHz probe by an experienced radiologist. Scans were performed from both intercostal and subcostal sides, and standard images of the patient were taken supine. Ultrasonographic parameters such as anterior diameters of the liver, liver size, homogeneity, and echogenicity of the liver parenchyma and pancreas were examined.

Statistical analysis

All quantitative data were analyzed using descriptive tests and presented as mean ± SD. The percentages and frequencies of each item between the two groups were compared using Crosstabs and Chi-square tests. Mann–Whitney test was applied to compare the mean of non-parametric data between the two groups. Student's *t*-test was applied to compare the mean of all data with normal distribution between two groups. The correlation between quantitative variables was evaluated using Spearman correlation tests. Multivariate regression analysis was used to determine the role of different variables in predicting liver size. In this study, $P < 0.05$ was considered statistically significant. SPSS software (IBM, version 19) was applied to analyze data.

Results

Three hundred patients with fatty liver disease and 300 healthy controls were included. In total, 56.3% of patients had a mild grade of fatty liver. The baseline demographic and clinical data of the patients and controls have been shown in Table 1. The frequencies of males and females in both groups were 53.7 and 46.3%, respectively. No significant difference was found in the mean of age, height, and frequency of sex between the two groups. Patients had significantly higher weight (71.87 ± 13.42 kg vs. 80.17 ± 16.41 kg; $P < 0.001$) and BMI (28.90 ± 5.19 kg/m^2 vs. 25.73 ± 4.0 kg/m^2; $P < 0.001$) mean values than controls. The mean liver size was significantly higher in NAFLD patients compared to controls (149.05 ± 12.60 mm vs 134.51 ± 12.09; $P < 0.001$).

An increasing trend was observed for the higher liver size in patients with normal to the severe grade of fatty liver. Patients with a severe grade of the fatty liver exhibited a higher mean level of liver size than other groups ($P < 0.001$) [Table 2 and Figure 1].

One-way ANOVA: Post hoc-Tukey test was applied to compare the liver size mean value between all groups.

The relationship between liver size and gender is summarized in Table 3. A significant correlation was found between liver size and gender. In both NAFLD and control groups, the mean liver size was significantly higher in males than females ($P < 0.05$).

The Spearman correlation analysis between the liver size and other parameters has been presented in Table 4. A significant correlation was observed between the liver size with other parameters, including age, height, weight, and BMI. An increase in the mean age, height, weight, and BMI was significantly associated with a higher size of the liver in both patients and controls ($P < 0.05$).

The results of multiple linear regression analyses of different parameters for predicting the liver size have been summarized in Table 5. The results showed that age ($P = 0.037$), gender ($P < 0.001$), height ($P < 0.001$), BMI ($P = 0.008$), and steatosis ($P < 0.001$) are independent variables for predicting liver size.

Table 1: Comparison of the basic demographic and clinical of patients and controls

Variables	NAFLD	Controls	*P*
Age (Years)	45.78±11.5	45.18±12.07	0.53
Gender			
Males (%)	161 (53.7)	161 (53.7%)	1
Females (%)	139 (46.3%)	139 (46.3%)	
Height (cm)	166.39±8.57	166.87±8.09	0.49
Weight (Kg)	71.87±13.42	80.17±16.41	<0.001
BMI (Kg/m^2)	28.90±5.19	25.73±4.0	<0.001
NAFLD grade			
Mild (%)	169 (56.3)	-	
Moderate (%)	104 (34.7)	-	
Severe (%)	27 (9.0)	-	
Liver size (mm)	149.05±12.60	134.51±12.09	<0.001

Discussion

In this study, the size of the liver was compared between patients with NAFLD and healthy controls. Our findings showed that patients with NAFLD had significantly higher mean weight and BMI values than controls. Similarly, Sheng *et al.*[17] reported that the mean clinical indicators, including age, height, weight, BMI, and waist circumference, were significantly higher in patients with NAFLD than in those without fatty liver. We did not find a significant difference in mean age or sex between the two groups. Our results indicate that an increased BMI is a major risk factor for NAFLD. To support this statement, previous studies demonstrated that NAFLD is closely associated with the risk of metabolic syndrome disorders such as weight gain and BMI.[18] It has also been reported that about 80% of patients with NAFLD are obese and have a high BMI.[19-21] However, these studies did not compare liver size between normal and NAFLD groups. Furthermore, the relationship between liver size and fatty liver grades has not been elucidated. As a result, we conducted this study to evaluate the size of the liver in healthy people and NAFLD patients and the relationship between the size of the liver and fatty liver grades [Figures 2 and 3].

According to our findings, the average liver size in patients with NAFLD is substantially larger than in the control group. Some previous research has investigated the size of the liver in fatty liver patients. For example, Cruz *et al.*[22] demonstrated that patients with fatty livers had a larger liver size than normal groups (15.0 cm vs 14.0 cm). Similarly, Patell *et al.*[23] discovered that the average liver size in NAFLD patients was substantially larger than that in the control group (153.6 mm vs 121.08 mm). In another study, Patzak *et al.*[11] revealed that patients with NAFLD grades I and II had significantly larger liver sizes than healthy controls. Also, it has been reported that the liver size in patients with NAFLD decreased significantly after two months of treatment with oral phosphatidylcholine.[24] These findings point to a direct and significant link between the size of the liver and the presence of fatty liver. As a result, regularly considering the liver's size may help predict and identify fatty

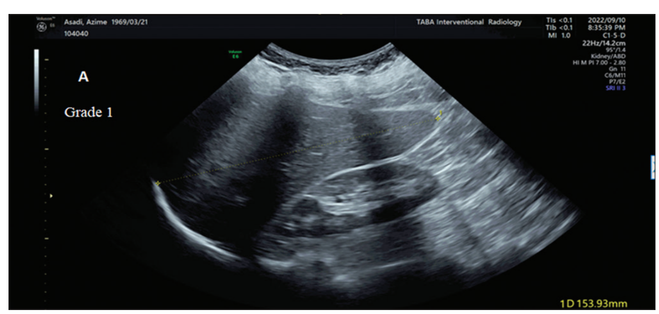

Figure 1: Liver measurement on ultrasonography (fatty liver Grade 1)

Table 2: The relationship between the liver size and NAFLD grade

	Normal	Mild grade	Moderate grade	Severe grade	*P*
Liver size (mm)	134.51±12.09^c	144.34±11.35^b	154.21±10.84^a	158.63±13.45^a	<0.001

The mean of the liver size was in order a>b>c. One-Way ANOVA: Post Hoc-Tukey test was applied to compare the liver size mean value between all groups

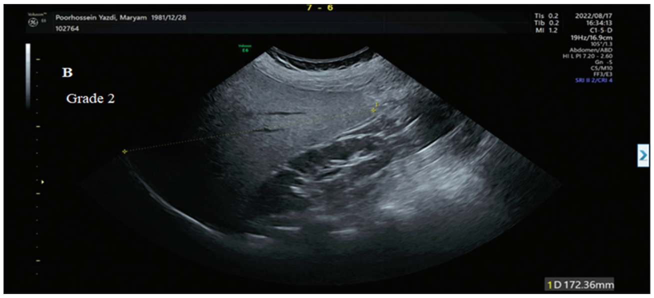

Figure 2: Liver measurement on ultrasonography (fatty liver Grade 2)

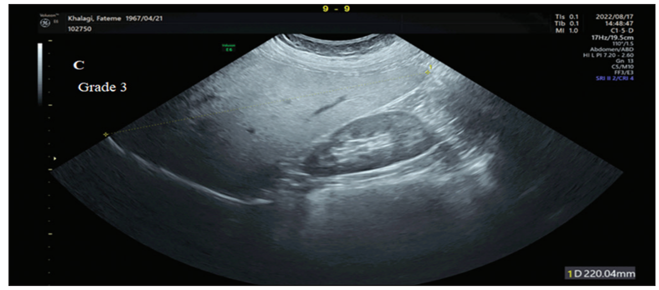

Figure 3: Liver measurement on ultrasonography (fatty liver Grade 3)

Table 3: The relationship between the liver size and gender

	NAFLD	Control	*P*
Gender			
Males	150.99±12.28	136.64±11.63	<0.001
Females	146.80±12.63	132.04±12.19	<0.001
P	0.02	0.002	

Table 4: The Spearman correlation analysis between the liver size and other parameters in each group

Parameters	NAFLD	Control
Age	*P*=0.025 *r*=0.092	*P*=0.032 *r*=0.124
Height	*P*<0.001 *r*=0.580	*P*<0.001 *r*=0.646
Weight	*P*<0.025 *r*=0.499	*P*<0.025 *r*=0.508
BMI	*P*<0.025 *r*=0.241	*P*<0.025 *r*=0.204

Table 5: Multiple linear regression analysis of different parameters for predicting the liver size

Variables	Unstandardized Coefficients B	Standardized Coefficients Beta	CI 9% for Beta	*P*
Weight	-0.434	-0.470	(-0.98, 0.08)	0.098
Height	172.885	1.00	(124.14, 221.62)	<0.001
Steatosis	-3.386	-0.340	(-4.27, -3.1)	<0.001
Gender	9.715	0.338	(7.64, 11.76)	<0.001
BMI	1.947	0.666	(0.5, 3.38)	0.008
Age	0.069	0.057	(0.004, 0.13)	0.037

liver. Given that hepatomegaly can be caused by various factors, including hepatic sinusoidal dilatation, high venous pressure and congestion, fat accumulation in liver cells and fibrosis, and glycogen distention of liver cells, early diagnosis, and identification of the primary causes of hepatomegaly are critical for disease treatment.[25,26]

This study also found a significant trend for a larger liver size from mild to severe grade of fatty liver. Similarly, Khanal *et al.*[10] reported a significant relationship between increased fatty liver grade and liver size and NAFLD patients' BMI. Therefore, these data support the idea that progress in NAFLD severity is associated with larger liver size.

A significant relationship was observed between liver size and sex in the present study. The mean liver size was significantly higher in men than in women. Similarly, Singh and Singla[14] demonstrated that the mean liver size in men is higher than in females (14.6 cm vs 12.79 cm). We also found that age, height, weight, and BMI are associated factors predicting liver size. Some studies reported the relationship between age and BMI with liver size. For example, Kratzer *et al.*[27] revealed that BMI and height were the most important factors influencing liver size. They also found that the size of the liver is larger in men and younger individuals than in women and older people. However, they did not consider the effect of fatty liver and its severity on liver size. In another study, Patzak *et al.*[11] showed that sex, age, height, weight, BMI, fatty liver, and metabolic syndrome influence liver size. While age was negatively correlated to the size of the liver, a positive association was observed between weight, height, BMI and liver size. Another study showed a significant relationship between the liver size with age, weight, BMI, and waist circumference in overweight/obese children and adults.[28] Ahmad *et al.*[29] found a relationship between sex, age, BMI, and liver size. According to the previous accomplished data and findings of the present study, ultrasound examination of the liver size can predict the occurrence of fatty liver. Furthermore, this is a non-invasive, simple, and available method for routine liver size screening in a population.

Conclusion

In conclusion, the findings of this study revealed that patients with fatty liver have a much larger liver than healthy individuals. Sex, age, BMI, weight, height, fatty liver disease, and higher steatosis grade are all liver size predictors. Therefore, examining liver size by ultrasonography can help as a simple and safe method for routine fatty liver screening. Since ultrasonography is an important imaging technique for diagnosing and grading fatty liver, it can be considered a non-invasive, lower cost, and the first-line imaging modality in evaluating fatty liver. Therefore, an essential measurement of liver size by ultrasonography can also be used in the management and treatment response evaluation in patients with fatty liver. The current study, however, has certain limitations. This study covered a small number of patients with a severe fatty liver grade. The severity of hepatic steatosis was diagnosed only through ultrasound examination; no other methods, such as fibroscan or MRI, were used. Other risk factors for liver size, such as smoking, diabetes, and lipid profile, were not considered. Therefore, further population-based studies are necessary to consider the effect of various risk factors on liver size.

Ethics approval and consent to participate

IR.AJUMS.HGOLESTAN.REC.1399.174.

Availability of data and materials

The datasets generated and/or analyzed during the current study are available in the [PubMed, Web of Science, Scopus, EM Base] repository.

Acknowledgements

We wish to thank all our colleagues in Allied Health Sciences School, Ahvaz Jundishapur University of Medical Sciences.

Authors' contributions

M.Kh conceived the manuscript and revised it. M.S, M.Gh, Z.F, and M.H done the statistical analysis, wrote the manuscript, and prepared tables and figures. All authors have read and approved the manuscript.

Financial support and sponsorship

Nil.

Conflicts of interest

The authors declare no conflict of interest. All procedure performs in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or compare ethical strand.

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